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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,358	MIGALY, PETER	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,41-43 and 48-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,41-43 and 48-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *August 27, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted August 27, 2007 wherein claims 1-3, 6, 9, 10, 14-37, 41-43, 48, 49, 51-55, 57, 59-62, 65, 71, 73, 74, 95-105, and 107-118 are amended, new claims 119-130 are introduced, and the specification is amended to incorporate material taken from the provisional application 60/319436. This application claims benefit of provisional application 60/319436, filed July 30, 2002.

Claims 1-38, 41-43, and 48-130 are pending in this application.

Claims 1-38, 41-43, and 48-130 as amended are examined on the merits herein.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 27, 2007 has been entered.

Applicant's amendment, submitted August 27, 2007, with respect to the rejection of instant claims 55, 57, 60, and 63-108 under 35 USC 112, first paragraph, for lacking written description for a method comprising administering the disclosed drugs to all patients treated by the practitioner, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to specify that the

patient population is all patients treated by the practitioner who are suffering from major depressive disorder or unipolar depression. Therefore the rejection is withdrawn.

Applicant's amendment, submitted August 27, 2007, with respect to the rejection of instant claims 55, 57, 60, and 63-108 under 35 USC 112, first paragraph, for lacking enablement for a method comprising administering the disclosed drugs to all patients treated by the practitioner, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to specify that the patient population is all patients treated by the practitioner who are suffering from major depressive disorder or unipolar depression. Therefore the rejection is withdrawn.

Applicant's amendment, submitted August 27, 2007, with respect to the rejection of instant claims 43, 98, 109, and 110 under 35 USC 112, first paragraph, for lacking enablement for a method of preventing depression, relapse of depression, or suicide, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to remove references to prevention. Therefore the rejection is withdrawn.

Applicant's arguments, submitted August 27, 2007, with respect to the rejection of instant claims 3-38, 49-52, 54, 56, 58, 61-94, and 97-107 under 35 USC 112, second paragraph, for reciting the indefinite term, "low dose," has been fully considered and found to be persuasive to remove the rejection as Applicant's definition of "low dose" as

25-50 mg chlorpromazine equivalent, recited on pp. 14-15 of the instant specification, is seen to adequately define a "low dose". Therefore the rejection is withdrawn.

Applicant's arguments, submitted August 27, 2007, with respect to the rejection of instant claims 1-6, 9, 11, 13, 14, 16-18, 20-22, 24-26, 28-30, 32-37, 41-43, 48, 49, 51, 53-68, 70, 72, 73, 75-77, 79-81, 83-85, 87-89, 91-104, and 109-118 under 35 USC 103(a) for being obvious over Tollefson et al., has been fully considered and found to be persuasive to remove the rejection as Tollefson is not seen to disclose a method of treating non-treatment-resistant depression. In particular, the phrase "rapid onset treatment of depression" is seen to refer to treatment of treatment-resistant depression, as disclosed in the clinical trial on pp. 21-22 of Tollefson. Therefore the rejection is withdrawn.

Applicant's arguments, submitted August 27, 2007, with respect to the rejection of instant claims 8, 19, 27, 31, 78, 82, 86, and 90 under 35 USC 103(a) for being obvious over Tollefson et al. in view of Kelleher et al., has been fully considered and found to be persuasive to remove the rejection as Tollefson is not seen to disclose a method of treating non-treatment-resistant depression. In particular, the phrase "rapid onset treatment of depression" is seen to refer to treatment of treatment-resistant depression, as disclosed in the clinical trial on pp. 21-22 of Tollefson. Therefore the rejection is withdrawn.

Applicant's arguments, submitted August 27, 2007, with respect to the rejection of instant claims 1-2, 4-6, 9-11, 13, 14, 37, 38, 42, 48, 51, 53-64, 66, 69, 70, 73, 96-104, and 109-118 under 35 USC 103(a) for being obvious over Faour et al., has been fully considered and found to be persuasive to remove the rejection as Faour is not seen to disclose a method of treating patients not suffering from psychosis. Therefore the rejection is withdrawn.

The following grounds of rejection of record in the previous office action are maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-12, 37, 38, 41-43, 48-50, 53-71, 95-103, and 126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal comprising administering certain antidepressants defined in the specification and prior art, does not reasonably provide enablement for such a method involving any antidepressant whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating depression and other disorders by administering a drug or a combination of two drugs. It is claimed that the antipsychotic drug improves the therapeutic outcome even in patients not suffering from psychotic symptoms.

The state of the prior art: Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art. Although a number of drug combinations have been tested and found to be useful, particularly combinations of a serotonin reuptake inhibitor with an atypical antipsychotic, many drugs of both types have not been tested. In particular, typical antipsychotics and dopamine system stabilizers such as aripiprazole have not been tested in the claimed methods. More generally, the full limits of the class of compounds known as "antidepressants" in the language of instant claim 1 have not been determined, and it is likely that there exist novel compounds with antidepressant activity that have not yet been discovered.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: In the absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because so many different compounds are known as antidepressants no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally. Thus the effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is unpredictable.

The Breadth of the claims: The claimed invention encompasses combination therapies of any "newer" antidepressant with an antipsychotic. The newer antidepressants are defined only in the negative, as not being a tricyclic or tetracyclic antidepressant or a permanent inhibitor of monoamine oxidase. In particular, a vast number of different possible modes of action for an antidepressant are recited in instant claim 12.

The amount of direction or guidance presented: Two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-17)

The presence or absence of working examples: No working examples of the claimed therapeutic methods is provided by Applicant.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as antidepressant/antipsychotic combination therapy. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would be required to determine the extent of antidepressants useful in said methods. Because Applicant has provided no working examples, and because the state of the art is unpredictable, many different antidepressants would need to be tested in order to provide a comprehensive understanding of which combinations are or are not useful in the claimed method. Because there is no structural limitation to the full scope of "newer antidepressants" one skilled in the art would have to discover each and every possible compound with antidepressant activity. Doing so would require the synthesis and testing of an enormous number of compounds. In the process of synthesizing the compounds to be tested, many novel and unpredictable synthetic methods would have to be developed. These experiments would be repeated many times in animal models of depression, cognitive distortions, and nicotine addiction, in order to establish their suitability as therapeutic methods. It should be noted that evaluating psychological disorders such as depression and cognitive distortions in animals is more difficult than evaluating a therapy for a nonpsychological condition such as cancer or arthritis. Animal experiments include, along with the actual administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the

animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated many times, and involve the maintenance, killing, and disposal of many experimental animals, to establish the suitability or lack thereof for each compound found to possess the desired activity in vitro.

The scale of synthesis, *in vitro*, and *in vivo* testing described in the preceding paragraphs would present an undue amount of unpredictable experimentation to require of anyone wishing to practice the invention.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention with every possible antidepressant.

Response to Argument: Applicant's arguments, submitted August 27, 2007, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Note that Applicant's arguments with respect to the terms "typical antipsychotic," "atypical antipsychotic," "and dopamine system stabilizer,"

are found to be persuasive and the rejected claims are not rejected for lacking enablement for the claimed classes of antipsychotics. The above rejection is maintained as applied to the term, "newer antidepressant." Applicant argues that this definition of a newer antidepressant is sufficiently well-defined to limit the claimed invention to an enabled class of compounds. However, the definition is still open-ended and not drawn to a class of compounds whose synthesis and use is enabled by the specification and/or the prior art.

Applicant further argues that functional language was allowed in European patent application EP 0966967. This is not relevant to the present prosecution as each patent application is prosecuted on its own merits, and furthermore US patent applications, prosecuted by the US Patent and Trademark Office, are not prosecuted using the same rules as those used by the European Patent Office.

Furthermore, Applicant argues that the allowability of customary English words such as "chair" or "table" in patent claims indicates that customary terms in the medical art such as "antidepressant" can also be used. However, the complexity of the chemical and pharmaceutical art raises the bar for enablement, and claims covering novel, undiscovered pharmaceutical entities are more difficult to enable than novel types of furniture. Inventing a new table or chair does not carry the burden of unpredictable experimentation that is associated with inventing a new drug. Therefore the term "antidepressant" or "newer antidepressant" is not seen to be enabled.

For these reasons the rejection is deemed proper and maintained.

Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted January 8, 2007 with respect to claim 65 has been fully considered and but is deemed to insert **new mater** into the claims since the specification as originally filed does not provide support for the active metabolite of risperidone. As the instant specification as filed contains no description of said metabolite or a method of using it as a therapeutic agent, the specification as originally filed does not provide support for the subject matter of instant claim 65. See *in re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

Response to Argument: Applicant's arguments, submitted August 27, 2007, with respect to the above ground of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that administering the metabolite of a drug is a logical and inherent step involved in administering the drug itself, as described fir the case of grape juice being an inherent product consumed when eating grapes. However, even in the case of grapes and grape juice, it is well recognized that fruit juices are not nutritionally equivalent to whole fruit, which contains components such as skin and pulp that provides additional nutritional value beyond what is obtained from merely drinking the juice. Furthermore, the sensory qualities of fruit juice and fruit differ significantly, and the juice is less effective at producing satiety than the whole fruit.

These examples serve to demonstrate that even in a case as simple as the extraction of juice from fruit, isolation of one particular product from a starting material can lead to significant changes in the function of the product.

Analogously, the biological effects of administering a drug are expected to differ form those of administering a metabolite of that drug. For example, the metabolite might be absorbed at a different rate or not at all. It may possess a more rapid onset of action or be inactivated or eliminated more quickly than the parent compound. There may be more than one active metabolite, each of which affects the subject differently. For these very reasons, there is a significant interest in prodrugs as novel pharmaceutical entities. If administering a compound were inherently identical to administering its active metabolite, there would be no incentive to spend time and money researching a prodrug that would be pharmaceutically indistinguishable from the known active metabolite.

Therefore the rejection is deemed proper and maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, 109-122, 124, and 126-130 are rejected under 35 U.S.C. 103(a) as

being obvious over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a D4 receptor antagonist, (an antipsychotic) and a pharmaceutically acceptable carrier. (p. 1, left column, paragraph 0002) Note that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Phobias and panic disorders are also considered to be cognitive distortions. General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and monoamine oxidase inhibitors, among others, as described in instant claims 11-13. Selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, and sertaline. (p. 3, paragraph 0025) Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15. Other useful antidepressants are listed in paragraph 0181 on p. 8. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Various dopamine D4 receptor antagonists can be used, as listed on pp. 15-21. In particular, p. 20, paragraph 0446 lists olanzapine as a useful D4 receptor antagonist. D4 receptor antagonists can be administered in a preferred dose of about 5 to about 500 mg per day. (p. 22, paragraph 0459) Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a

physician or other health care provider. Chappell et al. does not disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell et al. already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.
It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Chappell et al. using a dose of 5-10 mg of olanzapine per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Chappell et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's argument, filed August 27, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that Chappell et al. does not provide sufficient guidance or enablement to allow one of ordinary skill in the art to practice a method for treating non-treatment-resistant, non-psychotic depression by administering the claimed combination as initial therapy. However, the art is sufficiently predictable as regards known antidepressants and antipsychotic agents, as discussed at length by Applicant in his arguments with respect to the enablement of the claimed invention and the ability of one of ordinary skill in the art to practice off-label administration of known antipsychotic agents, that one of ordinary skill in the art would have been able to reliably use a known agent for these indication even without a detailed study providing exhaustive detail as to the effects in each and every possible indication. One of ordinary skill in the art would have recognized how to practice the claimed invention given the disclosure by Chappell et al. that these pharmaceutical combinations are suitable for the treatment of depression and/or anxiety, including those cases of depression and/or anxiety demonstrating neither psychosis nor treatment resistance. P. 1, paragraphs 0006-0007 of Chappell et al. explicitly recite a list of various types of depression including major depressive disorder. The test for obviousness in patent prosecution is not the same as that used in the approval of treatments by the Food and Drug Administration, or that used in deciding malpractice suits. It is not required that the treatment be shown to be equivalent to or better than other available treatment options. All that is required is that it be available as one possible option for consideration by the person of ordinary skill in

the art. Weighing the risks and benefits of different therapeutic options is the job of the person of ordinary skill in the art. The disclosure of Chappell et al. does indeed place the disclosed subject matter in possession of the public. It is noted that Applicant's own specification provides no actual working examples or experimental studies of the claimed treatment, but merely suggests that, given the existence of treatment-resistant depression and the danger of suicide in depressed patients, a skilled practitioner could, weighing the risks and benefits, choose to administer an antipsychotic with an antidepressant as initial therapy in order to reduce the overall risk of suicide. Applicant's own reasoning would be open to the same charges of malpractice as those alleged for Chappell et al. This risk-benefit analysis is not something novel or unobvious to one of ordinary skill in the art. Therefore, one of ordinary skill in the art would in fact be enabled to practice the claimed method based on Chappell et al.

Applicant further argues that Chappell et al. does not teach all of the claimed steps. The only steps recited in the claims as currently pending involve administering a combination of an antidepressant and an antipsychotic to a patient, wherein the patient suffers from non-treatment-resistant, non-psychotic depression, and the treatment is administered as soon as possible. All of these claim elements are either taught by Chappell et al., or obvious to one of ordinary skill in the art. (as is the case for administering treatment as soon as possible. Therefore it is unclear which additional steps applicant has introduced. The intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding

suicidal ideation, and delaying or resisting relapse, are inherently present in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at elevated risk for suicide, and could suffer relapse after treatment.

Applicant also argues that Chappell et al. does not disclose a low dose for any of the disclosed antipsychotics, and that the recited dose range includes amounts that are much higher than the claimed dose. However, one of ordinary skill in the art would naturally be motivated to use the lowest effective dose within the disclosed dose range, given the dangerous side effects of antipsychotic drugs.

Further, Applicant argues that Chappell et al. discloses merely a broad range of conditions, such as "depression" or "anxiety" rather than the specific indications claimed in the instant claims. This is not the case. Chappell et al. specifically recites specific types of depression and anxiety, for example, major depressive disorder, that fall within the terms "major depressive disorder" and "unipolar depression". Given this disclosure, it would have been obvious that the therapy can be applied to cases not demonstrating treatment resistance or psychosis. In fact, nowhere in the Chappell et al. reference is it said that the invention is specifically directed toward treatment-resistant depression. Psychosis is mentioned as an additional, distinct condition that can also be treated, but which does not have to be present when practicing the disclosed invention. It is also noted that Applicant's disclosure does not direct the clinician to not administer the therapy to psychotic or treatment-resistant cases, but rather to administer treatment to

everyone without considering psychosis or treatment resistance. This is the same scope of disclosure as Chappell et al.

Therefore the rejection is deemed proper and maintained.

Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) in view of Berman et al. (Reference of record in previous action) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell et al. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's argument, filed August 27, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to

remove the rejection. Applicant argues that ketamine has severe side effects and therefore would not be used by one of ordinary skill in the art as an antidepressant. However, as discussed above, according to MPEP 2123, nonpreferred embodiments of the prior art are equally valid as prior art. "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) The mere fact that one of ordinary skill in the art would have known of compounds that produced fewer side effects than ketamine does not mean that the use of ketamine as an antidepressant is non-enabled. In fact, Berman et al. discloses a successful clinical treatment of depression in human subjects using ketamine, which is sufficient enabling disclosure to practice this therapeutic method.

Furthermore, Applicant argues that the failure of those of ordinary skill in the art to use ketamine as an antidepressant in the five years since the publication of the cited references is indicative of secondary factors proving nonobviousness. According to *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004), "[a]bsent a showing of a long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." 392 F.3d at 1324-25, 73 USPQ2d at 1229-30. See MPEP 2144.05 (B.III). Applicant does not show a long-felt need for a new antidepressant, or the failure of others to use ketamine as an antidepressant. In fact, Applicant's disclosure provides no new data, information, or reasoning about ketamine that would contribute to what is known in the art about this drug, or to indicate that ketamine is particularly useful in the claimed

combination therapy. Therefore there is nothing novel, non-obvious, or unexpected about Applicant's proposed use of ketamine in the claimed invention.

For these reasons the rejection is deemed proper and maintained.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 126-128 are rejected under 35 U.S.C. 102(b) as being anticipated by Robertson et al. (Reference of record in PTO-892) Robertson et al. discloses a number of studies of the antidepressant activities of major tranquilizers (also known as typical antipsychotics). (p. 173, last paragraph) In particular, perphenazine and combinations of perphenazine with amitriptyline were used in treating patients suffering from depression, including non-psychotic depression. (p. 179, paragraphs 4-5) Perphenazine was found in one study to be particularly effective, while a combination of perphenazine and amitriptyline was found to be effective for treating other types of depression. It is noted that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Flupenthixol, (p. 183, paragraphs 4-6) and sulpride, (p. 185, paragraphs 1-2) are also seen to possess antidepressant activity. The

intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation, and delaying or resisting relapse, are inherently present in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at elevated risk for suicide, and could suffer relapse after treatment.

Therefore the claimed invention is anticipated by Robertson et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91-94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Schmidt et al. (Reference of record in PTO-892) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using ziprasidone, risperidone, or quetiapine as the antipsychotic agent.

Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 198, table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ziprasidone, risperidone, or quetiapine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 5, 9, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Reference of record in PTO-892) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using risperidone, trifluoroperazine, or zotepine as the antipsychotic agent.

Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) In particular, risperidone, olanzapine, trifluoroperazine and zotepine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use risperidone, trifluoroperazine, or zotepine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1-3, 9, 11-15, 37, 38, 41-43, 48, 49, 53-62, 69-74, 96-105, and 129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in PTO-892) as applied to claims 126-128 above, and further in view of the Merck Manual of Diagnosis and Therapy, Seventeenth Edition. (Reference included with PTO-892, herein referred to as Merck) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a therapy comprising a combination of a typical antipsychotic with a newer antidepressant. (i.e. an antidepressant that is not a tricyclic or tetracyclic antidepressant or a MAO inhibitor) Robertson et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a

physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Robertson et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Robertson et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Robertson et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in PTO-892) in view of Berman et al. (Reference of record in previous action) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Robertson et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Robertson et al., namely treating depression. One of ordinary skill in the art would

reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's argument, filed August 27, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection, for reasons recited as regards the rejection over Chappell et al. in view of Berman et al.

Claims 1, 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48, 49, 51-64, 66, 70-77, 79-81, 83-85, 87-89, 91-105, 109-122, and 124-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pivac et al. (Reference included with PTO-892) in view of Merck (Reference included with PTO-892) Pivac et al. discloses that atypical antipsychotics such as risperidone or olanzapine, should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph) Pivac et al. does not disclose a therapeutic method using the specific SSRIs fluoxetine, paroxetine, sertaline, or fluvoxamine, or the atypical antipsychotics ziprasidone or quetiapine. Pivac et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants

recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. Merck et al. also discloses a listing of atypical antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone. (p. 1570, table 193-4)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the various SSRIs and atypical antipsychotics disclosed by Merck in the method of Pivac et al. One of ordinary skill in the art would have recognized that the specific compounds disclosed by Merck fall within the broad classes described by Pivac et al., and can thus be used in the disclosed method. Substituting these known prior art compounds in a known prior art method is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Pivac et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Pivac et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been

motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1-4, 7, 8, 10-15, 19, 23, 27, 31, 36-38, 41-43, 48, 49, 51-63, 67, 68, 70-74, 78, 82, 86, 90, 95-105, 109-122, and 124-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (PCT international publication WO02/060423, reference included with PTO-892) in view of Merck. (Reference included with PTO-892) Jordan et al. discloses a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor, comprising administering a compound having a given structure. (p. 15, lines 5-18) According to the Chemical Abstracts Registry entry 129722-12-9, (reference included with PTO-892) this structure is aripiprazole. This compound is useful for treating various disorders of the central nervous system, for example major depression and melancholia, as well as various cognitive distortions including obsessive compulsive disorder, alcohol and drug addiction, and cognitive impairment. (p. 16, line 23 – p. 17, line 10) The preferred unit dosage form is 1-20 mg of active agent. (p. 18, lines 5-10) Jordan et al. does not disclose a method comprising administering aripiprazole in combination with an antidepressant. Jordan et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to

a physician or other health care provider, or a method comprising administering 2.5-15 mg of aripiprazole.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Jordan et al. to a patient suffering from major depression either alone or complicated by any of the various cognitive distortions recited by Jordan et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Jordan et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Jordan et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success

because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Jordan et al. using a dose of 2.5-15 mg of aripiprazole per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Jordan et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Thus the invention taken as a whole is *prima facie* obvious.

Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (Reference of record in PTO-892) in view of Berman et al. (Reference of record in previous action) The disclosure of Jordan et al. is discussed above. Jordan et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Jordan et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Jordan et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 3-5, 9-15, 20, 28, 37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Theobald et al. (US patent publication 2003/0049308, first published as PCT international publication WO01/80837) Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating nicotine dependency, for nicotine substitution, or for disaccustoming smokers. (p. 1, paragraphs 0002, 0003, and 0009) The additional active agent can include antidepressants or neuroleptics (antipsychotics), for example chlorpromazine, perphenazine, sulpride, clozapine, clomipramine, doxepin, risperidone, paroxetine, or fluvoxamine. (p. 2, paragraphs 0015-0017) Theobald et al. does not explicitly exemplify a method comprising administering said patch comprising nicotine, an antidepressant, and an antipsychotic.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Theobald et al. using nicotine in combination with both an antidepressant and an antipsychotic. One of ordinary skill in the art would have been motivated to practice the invention in this manner because each of the additional agents (the antidepressant and the antipsychotic) is revealed individually by Theobald et al. to be useful in combination with nicotine for the treatment of nicotine addiction. Adding both of these agents at once to the disclosed invention is well within the ordinary and routine level of skill in the art and carries a reasonable expectation of success in achieving the desired therapeutic goal.

Thus the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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